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Preface
Acknowledgments

1 Stru

1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
1.10
1.11
1.12
1.13
1.14
1.15
1.16
1.17
1.18
1.19
1.20
1.21

each dissolved particle is a cluster of solvent molecules, held there by bonds; it was formation of these bonds that provided the energy needed to break the bonds that held solute particles to each other. The very fact that dissolution has taken place shows this: new bonds have replaced old ones.

The science of organic chemistry rests on a simple premise: that chemical behavior is determined by molecular structure. Yet, in solution all participants in a chemical reaction are solvated: the reactants and the products—and the *transition state*. Now, our basic approach to chemical reactivity is to consider energy differences between reactants and transition states; that is, we estimate relative stabilities of these species. We do this by examining—mentally and, by use of models, physically—the structures involved; this examination *must* include any solvent clusters that help make up those structures and help determine their stabilities.

In this chapter, using as our examples the nucleophilic substitution reactions we have just studied, we shall see how reactivity—and, with it, the course of reaction—is affected by the solvent. The solvent adds a new dimension to our study of organic chemistry; if it complicates things, it at the same time adds richness. It offers us the most practical way to *control* what happens in a chemical reaction. The effect exerted by a solvent is one kind of medium effect—environmental effect—and in that sense is just the beginning of a trail that leads all the way to the ultimate organic reaction, the action of an enzyme; this (literally) vital action is possible only because the substrate is *dissolved* in the enzyme, held to it by the same kinds of forces that a solvent uses.

Let us begin our study of the role of the solvent, then, by learning more about the kinds of bonds that are broken and formed when dissolution takes place.

7.2 Secondary bonding

In our discussion of melting, boiling, and solubility in Chapter 1, we looked briefly at the kinds of forces that act between molecules, between ions, and between molecules and ions. All of these, we said, are electrostatic forces—the attraction of positive for negative. These attractive forces—these *bonds*—are the following.

(a) **Ion-ion bonds:** the attraction between the opposite charges on a cation and an anion.



(b) **Dipole-dipole bonds:** the attraction between the positive end of one polar molecule and the negative end of another polar molecule.



The most powerful of these dipole-dipole bonds is the **hydrogen bond**, in which a hydrogen atom acts as a bridge between two electronegative atoms (F, O, N); it is held to one—the *hydrogen-bond donor*—by a covalent bond, and to the other—

the *hydrogen-bond acceptor*—



The strength of the hydrogen bond depends on the electronegativity of the bond donor and acceptor atoms. The strength of the hydrogen bond is about 1/10 that of a covalent bond. The electronegativity of the bond donor and acceptor atoms is left behind by the electronegativity of the bond donor and acceptor atoms. The electronegativity of the bond donor and acceptor atoms is what makes a hydrogen bond a stronger bond.

(c) **Van der Waals bonds:** the attraction between the positive end of one polar molecule and the negative end of another polar molecule.

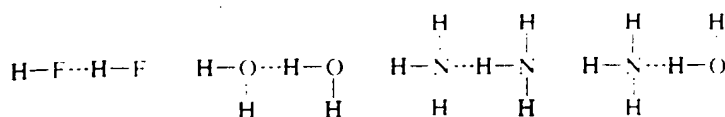
(d) **Ion-dipole bonds:** the attraction between a polar solvent molecule and a nonpolar molecule (Fig. 7.2).

Fig. 7.2

Except for the hydrogen bond, all other bonds are often called secondary bonds. In contrast to the primary bonds, secondary bonds are not formed together. Individual molecules are held together—and the secondary bonds are formed together—and the secondary bonds are formed together.

If this seems strange, it is because the hydrogen bond is so strong. At 1413°C, at room temperature, it is so strong that it is not the same.

the *hydrogen-bond acceptor*— by purely electrostatic attraction. For example:



The strength of a particular hydrogen bond depends upon the nature of the hydrogen-bond donor and of the hydrogen-bond acceptor. *A more acidic donor forms a stronger hydrogen bond.* The strength of a hydrogen bond depends upon how positive the hydrogen is (Sec. 1.19); acidity depends upon how well the conjugate base accommodates the electron pair left behind by the departed proton. Both of these properties are increased by the same factor: electron withdrawal in the group attached to the hydrogen. *A more basic acceptor forms a stronger hydrogen bond.* The strength of a hydrogen bond depends upon how negative the acceptor atom is—that is, how available its electrons are; and availability of electrons is what makes a molecule basic.

(c) **Van der Waals forces:** the attraction between the oppositely charged ends of momentary, induced dipoles in neighboring molecules. These forces act between all molecules, even non-polar ones.



(d) **Ion-dipole bonds:** the attraction of a positive ion for the negative end of a polar solvent molecule, and of a negative ion for the positive end of a polar solvent molecule (Fig. 7.1).

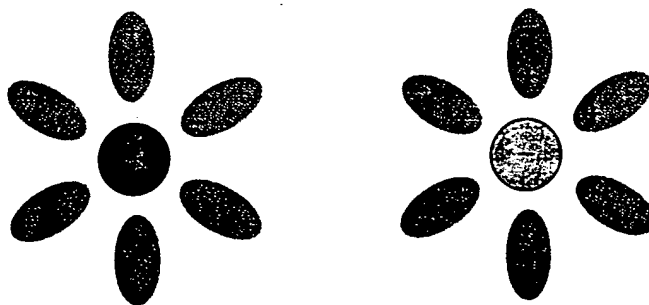


Figure 7.1 Ion-dipole interaction: solvated cation and anion.

Except for full-fledged ionic bonds in an ionic crystal, these attractive forces are often called **secondary bonds**. They act *between* different molecules and ions, in contrast to the covalent bonds that act *within* a molecule or ion and hold the atoms together. Individually, each secondary bond is relatively weak. But, acting together—and they work as a team—a collection of such bonds is extremely powerful; their formation, as we shall see, can supply enough energy to break a covalent bond.

If this seems surprising, remember this. To make sodium chloride boil, we must heat it to 1413°C; at room temperature we can dissolve it in a few moments by simply stirring it into a beaker of water. Yet the interionic forces being overcome in both processes are exactly the same.

In this chapter, we shall be primarily concerned with secondary bonding as it is involved in the action of the solvent: dissolving solutes, affecting their reactivity, and even, in a very direct way, reacting with them. But secondary bonding is involved in much more than solvent effects. These same forces, acting between the long, thread-like molecules of cotton, wool, silk, and nylon, give strength that is needed in the formation of fibers (p. 1095). Even the weakest of them, van der Waals forces, acting between non-polar chains of phospholipids, are the mortar in the walls of living cells (p. 1131).

Secondary bonding exists not only between different molecules but between different parts of the same molecule. In this way it plays a key role in determining the *shapes* of large molecules like proteins and nucleic acids, shapes that determine, in turn, their biological properties: the size of the "pockets" in the hemoglobin molecule, for example, just big enough to hold heme groups with their oxygen-carrying iron atoms (p. 1228); the helical shape of α -keratin and collagen molecules that makes wool and hair strong, and tendons and skin tough (p. 1225). It is secondary bonding that makes the double helix of DNA *double*—and thus permits the self-duplication of molecules that is the basis of heredity (p. 1244).

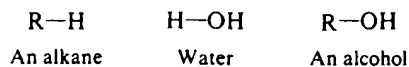
And so, our study in this chapter will have two aims: to understand better the role of the solvent; and, at the same time, to understand better the nature of secondary bonding.

7.3 Solubility: non-ionic solutes

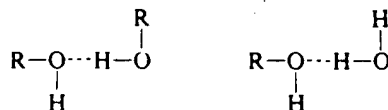
The solubility characteristics of non-ionic solutes, we said earlier (Sec. 1.21), depend chiefly upon their polarity—and in particular their ability to form hydrogen bonds. "Like dissolves like" is our rule-of-thumb.

Let us consider the kinds of compounds we have already encountered, beginning with hydrocarbons and alkyl halides. These are non-polar or weakly polar, and dissolve in solvents of similar polarity: in hydrocarbons like ligroin or benzene; in alkyl halides like chloroform and carbon tetrachloride; in diethyl ether. The forces holding the solute molecules to each other—and the solvent molecules to each other—are readily replaced by very similar forces holding solute molecules to solvent molecules. Hydrocarbons and alkyl halides do not dissolve in water, whose molecules are highly polar and held strongly to each other by hydrogen bonds.

Next, let us turn to alcohols. Structurally, we have seen, an alcohol is a composite of an alkane and water: it contains an alkane-like alkyl group and a water-like hydroxyl group.



The hydroxyl group is quite polar and, most important, contains hydrogen attached to the highly electronegative element oxygen. Through the hydroxyl group, alcohols are capable of forming hydrogen bonds: hydrogen bonds to each other, which give alcohols abnormally high boiling points (Secs. 1.20 and 6.5);



hydrogen bonds to other molecules, which tend to make alcohols soluble in other hydroxyl compounds, such as water. For the smallest alcohol, methanol (CH_3OH), we have seen, the result is complete solubility in water (Sec. 1.21). Hydrogen bonds between water and methanol molecules readily replace the very similar hydrogen bonds between different methanol molecules and different water molecules.

Now, because of the very special status of water as a solvent—especially in biological systems—the terms *hydrophilic* (water loving) and *hydrophobic* (water hating) are used in reference to water solubility and water insolubility. Instead of hydrophobic, the term *lipophilic* (fat loving) is often used; this emphasizes not so much insolubility in water as solubility in non-polar solvents. Thus, methanol is hydrophilic, and alkanes and alkyl halides are lipophilic (or hydrophobic).

Since it is easier to work with a term for a positive quality than one for a negative quality, in this book we shall generally use *lipophilic*. This term is meant simply to indicate the fact of solubility in non-polar solvents. It may well be—as is widely held—that this solubility is chiefly due to rejection by water rather than positive acceptance by a non-polar solvent.

Next, let us consider a series of alcohols, and the effect of the alkyl group on solubility. Where the hydroxyl group is hydrophilic, the alkyl group is lipophilic. Table 7.1 gives the water solubility of a series of alcohols. For the lower members of the series, the $-\text{OH}$ group constitutes a large portion of the molecule, and these compounds are miscible with water. But, we see, as the number of carbons increases, the solubility steadily decreases; a long chain with an $-\text{OH}$ at one end of it is mostly hydrocarbon, and its solubility shows this. (See Fig. 7.2, on the next page.)

Table 7.1 SOLUBILITY OF ALCOHOLS IN WATER

Alcohol	Solubility, g/100 g H_2O
CH_3OH	∞
$\text{CH}_3\text{CH}_2\text{OH}$	∞
$\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$	∞
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	7.9
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	2.3
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	0.6
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	0.2
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$	0.05

Now, if a molecule is big enough—if an alcohol, say, has a chain of 16 to 20 carbons or more—hydrophilic and lipophilic parts display their individual solubility properties. The hydrophilic parts dissolve in water; the lipophilic parts dissolve in a non-polar solvent or, if there is none about, cluster together—in effect, dissolve in each other. Such dual solubility behavior gives soaps and detergents their cleansing power (Secs. 33.4 and 33.6), and controls the alignment of molecules in cell membranes (Sec. 33.9); a globular protein molecule—an enzyme, say—coils up to expose its hydrophilic parts to the surrounding water and to hide its lipophilic parts, and in doing this takes on the particular shape needed for its characteristic biological properties (Sec. 36.11).

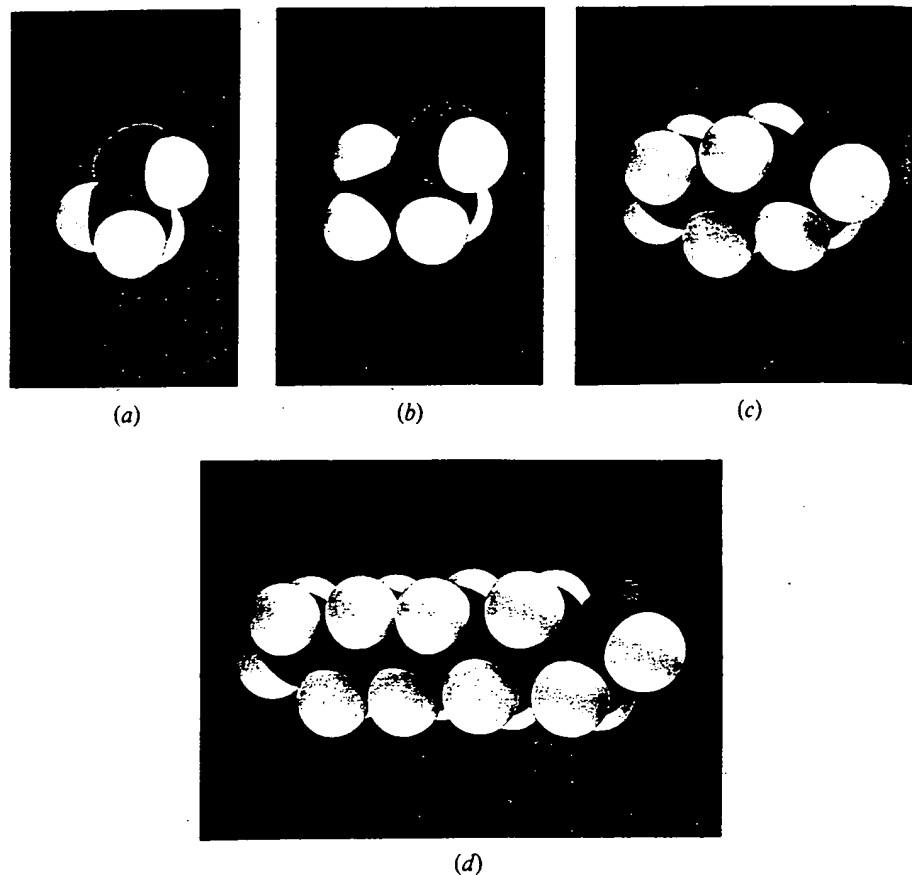


Figure 7.2 Molecular structure and physical properties: solubility. (a) Methyl alcohol, (b) ethyl alcohol, (c) *n*-butyl alcohol, and (d) *n*-octyl alcohol. As the alkyl group gets bigger, the molecule becomes increasingly alkane-like and the water solubility decreases.

7.4 Solubility: ionic solutes. Protic and aprotic solvents. Ion pairs

Now let us turn to the dissolution of ionic compounds.

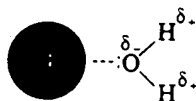
The forces holding together an ionic lattice are powerful, and a great deal of energy is needed to overcome them. This energy is supplied by the formation of many ion-dipole bonds between the ions and the solvent. About each ion there gathers a cluster of solvent molecules, their positive ends turned toward a negative ion, their negative ends turned toward a positive ion (Fig. 7.1, p. 251).

To dissolve ionic compounds, then, a solvent must be *highly polar*. In addition, we have seen, it must have a *high dielectric constant*; that is, it must be a good insulator, to lower the attraction between oppositely charged ions once they are solvated.

But water owes its superiority as a solvent for ionic substances only *partly* to its polarity and its high dielectric constant. There are other liquids that have very large dipole moments and high dielectric constants, and yet are very poor solvents for ionic compounds. What is needed is *solvating power*: the ability to form strong

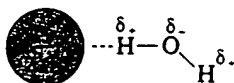
bonds to dissolved ions. Solvating power is not simply a matter of high dipole moment; it has to do with the nature of the ion-dipole bonds that are formed. To see what is meant by this we must look more closely at the structure of the solvent. Let us start with water.

Cations, we said, are attracted to the negative pole of a polar solvent. In water the negative pole is clearly on oxygen. Oxygen is highly electronegative and, most important, it has *unshared pairs of electrons*.



Furthermore, with only two tiny hydrogens attached to it, the oxygen is *well exposed*; a number of oxygen atoms in a number of water molecules can cluster closely about the cation without crowding.

Anions, we said, are attracted to the positive pole of a polar molecule. In water the positive poles are clearly on hydrogen. The ion-dipole bonds holding anions to water, we recognize, are *hydrogen bonds*.



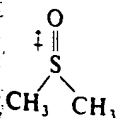
Hydrogen bonding permits particularly strong solvation of anions. Not only is there a strong positive charge concentrated on a very small atom, hydrogen, but this hydrogen juts out from the molecule and is well exposed; the anion can be held by a number of hydrogen bonds on a number of water molecules without crowding.

Thus, water owes a large part of its special solvating power to its —OH group: it solvates cations strongly through the unshared pairs on oxygen; it solvates anions strongly through hydrogen bonding.

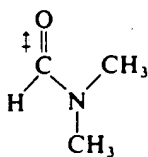
Methanol resembles water in having an —OH group. It is not surprising that it, too, dissolves ionic compounds. (It is, however, inferior to water. It is less polar, and the CH₃ group is bigger and causes more crowding than the second H of water.)

Solvents like water and methanol are called **protic solvents**: solvents containing hydrogen that is attached to oxygen or nitrogen and hence is acidic enough to form hydrogen bonds. Other protic solvents solvate ions in the same way that water does: *cations, through unshared pairs; anions, through hydrogen bonding*.

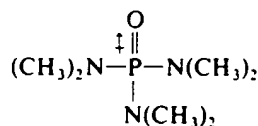
Recent years have seen the development and widespread use of polar **aprotic solvents**: solvents with moderately high dielectric constants, which do not contain acidic hydrogen. For example:



Dimethylsulfoxide
DMSO



Dimethylformamide
DMF



Hexamethylphosphorotriamide
HMPT

They dissolve ionic compounds, but in doing this their action differs in a very important way from that of protic solvents: *they cannot form hydrogen bonds to anions.*

These aprotic solvents are highly polar, with dipole moments several times as large as that of water. As indicated on the formulas, the negative pole in each of our examples is on an oxygen atom that juts out from the molecule (see Fig. 7.3). Through unshared pairs of electrons on these negatively charged, well-exposed atoms, cations are solvated very strongly.

The positive pole, on the other hand, is buried within the molecule. Through this shielded, diffuse charge, the molecule can solvate anions only very weakly. *Aprotic solvents thus dissolve ionic compounds chiefly through their solvation of cations.*

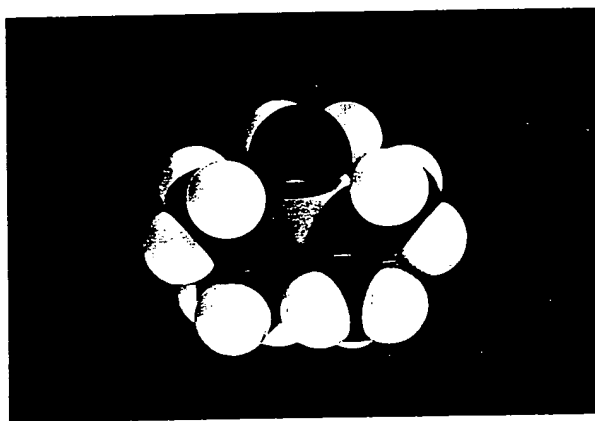


Figure 7.3 A polar aprotic solvent: hexamethylphosphorotriamide (HMPT). The molecule is shown with its positive pole, on the red oxygen atom, up, and the negative pole, on yellow phosphorus, down. As we see, oxygen juts out from the molecule, exposed and accessible; through its unshared pairs of electrons, it bonds strongly to cations. Phosphorus is buried within the molecule; its positive charge is shielded from the outside by bulky groups, and is only very weakly attracted to anions.

Now, as we have already seen for nucleophilic substitution, much of organic chemistry is concerned with reactions between non-ionic compounds (generally organic) and ionic compounds (inorganic and organic), and it is necessary to select a solvent in which both of the reagents will dissolve. Water dissolves ionic compounds very well, but it is a poor solvent for most organic compounds. Non-polar solvents—ether, chloroform, benzene—are good solvents for organic compounds, but very poor solvents for inorganic salts. Alcohols, particularly the smaller ones like methanol and ethanol, offer one way—the traditional way—out of this difficulty. Their lipophilic alkyl groups help them to dissolve non-ionic organic reagents; their hydroxyl groups permit them to dissolve ionic reagents. And so, alone or mixed with water, methanol and ethanol provide a medium in which, for example, nucleophilic aliphatic substitution has been commonly carried out.

But water and alcohols are protic solvents. Through hydrogen bonding, we have seen, such solvents solvate anions strongly; and anions, as it turns out, are usually the important half of an ionic reagent. Thus, although protic solvents dissolve the reagent and bring it into contact with the organic molecule, they also

the same time stabilize the anions and lower their reactivity drastically; their basicity is weakened and, with it, the related property, nucleophilic power (Sec. 5.8).

This is where aprotic solvents come in. Through their lipophilic portions, they dissolve organic compounds. They also dissolve inorganic compounds, but they do this, as we have just seen, chiefly through their solvation of cations. Anions are left relatively unencumbered and highly reactive; they are more basic and more nucleophilic.

By use of these aprotic solvents, dramatic effects have been achieved on a wide variety of reactions. Reactions that, in protic solvents, proceed slowly at high temperatures to give low yields may be found, in an aprotic solvent, to proceed rapidly—often at room temperature—to give high yields. A change to an aprotic solvent may increase the reaction rate as much as a millionfold.

Just as solvents differ in their ability to solvate ions, so ions differ in their tendency to be solvated. The concentrated charge on a small, "hard" ion leads to stronger ion-dipole bonding than the diffuse charge on a larger, "soft" ion. Thus, in a given solvent, F^- is more strongly solvated than Cl^- , and Li^+ is more strongly solvated than Na^+ .

There is an alternative way to view the stabilization of an ion by a solvent. According to the laws of electrostatics, we have seen (Sec. 5.20), the *stability of a charged system is increased by dispersal of charge*. Consider, for example, a solvated anion (Fig. 7.1). The positive ends of the solvent molecules are turned toward the anion and partially neutralize its charge; in doing this they are themselves partially neutralized. This leaves the solvent molecules with a net negative charge; that is, the outer, negative ends are no longer quite balanced by the inner, positive ends. The negative charge originally concentrated on the anion is now distributed over the very large outer surface of the solvent cluster. This amounts to a very large dispersal of charge and, with it, an enormous stabilization of the anion. In the same way, of course, cations are stabilized by dispersal of their positive charge over the solvent cluster.

Such dispersal is more important for the stabilization of a small ion like F^- or Li^+ than for a larger ion like I^- or Rb^+ , in which the charge is already dispersed over a considerable surface.

Dispersal of charge—either through solvation or within the ion itself—tends to stabilize organic cations and anions as well as inorganic ones. This concept plays a key role in our understanding of the large fraction of organic chemistry that involves such intermediate particles, as we have already begun to realize from our study of carbocations in Chapter 5.

So far in this section we have discussed the interaction of an ion only with the solvent. But there is another component of the solution to be considered. Each ion has a *counter-ion*, that is, an ion of opposite charge that is also necessarily present. In dilute aqueous solutions an inorganic ion is strongly solvated and effectively insulated from the charge of its counter-ion. But in a solvent of weaker solvating power or lower dielectric constant—in methanol, for example, or one of the aprotic solvents we have described—it feels this charge, and is attracted by it. There is a measure of ionic bonding, and the pair of oppositely charged ions is called an *ion pair*.

The strength of this ionic bonding depends upon the nature of the solvent. In solvents that solvate weakly, ionic bonding is strong; there are no solvent molecules between the pair of ions, and we speak of a *tight ion pair*. In solvents that solvate

strongly, ionic bonding is weak; a layer or layers of solvent molecules may separate the pair of ions, and we speak of a *loose ion pair*.

Ion pairs—organic as well as inorganic—play an exceedingly important part in organic chemistry. An ion in solution is subject to many forces, and the stabilizing effect of a counter-ion—like that of the solvent—is one that must always be reckoned with.

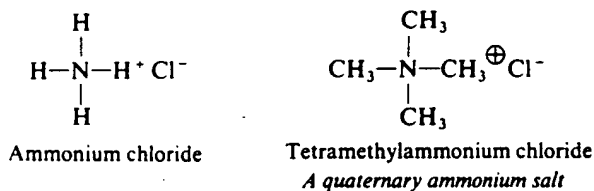
Problem 7.1 Label each of the following solvents as protic or aprotic:

- (a) $\text{NH}_3(\text{l})$ (b) $\text{SO}_2(\text{l})$ (c) CH_2Cl_2 (d) $\text{CH}_3\text{CH}_2\text{OH}$
 Ammonia Sulfur dioxide Methylene chloride Ethanol

- (e) $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$ (f) $\text{CH}_3\text{C}(=\text{O})\text{OH}$ (g) $\text{CH}_3\text{C}(=\text{O})\text{CH}_3$ (h) $\text{H}-\text{C}(=\text{O})-\text{NH}_2$
 Diethyl ether Acetic acid Acetone Formamide

- (i) $\text{H}-\text{C}(=\text{O})-\text{NH}-\text{CH}_3$ (j) $\text{CH}_3\text{C}\equiv\text{N}$ (k) $\text{C}_4\text{H}_8\text{O}$ (l) $\text{C}_4\text{H}_8\text{S}_2\text{O}_2$
N-Methylformamide Acetonitrile Tetrahydrofuran Sulfolane

Problem 7.2 Like most inorganic salts, ammonium chloride is insoluble in non-polar organic solvents. If the hydrogens of NH_4^+ are replaced by CH_3 groups, however,



the resulting salt shows appreciable solubility in these solvents. (a) How do you account for this contrast? (b) How might you increase the solubility still further?

Now let us see how what we have discussed so far comes into play in chemical reactions.

7.5 The $\text{S}_{\text{N}}1$ reaction: role of the solvent. Ion-dipole bonds

In discussing each of the reactions, $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}1$, we accounted for differences in reactivity among various substrates on the basis of differences in the amount of energy required: one substrate reacts faster than another chiefly because of a lower E_{act} . In $\text{S}_{\text{N}}1$, for example, the difference in rate between tertiary and secondary substrates corresponds to a difference in E_{act} of about 15 kcal.

But we have not taken up a more basic matter—one that involves much larger amounts of energy. How do we account for the fact that substitution occurs *at all* even for the most reactive substrates? By either mechanism, $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}1$, a bond